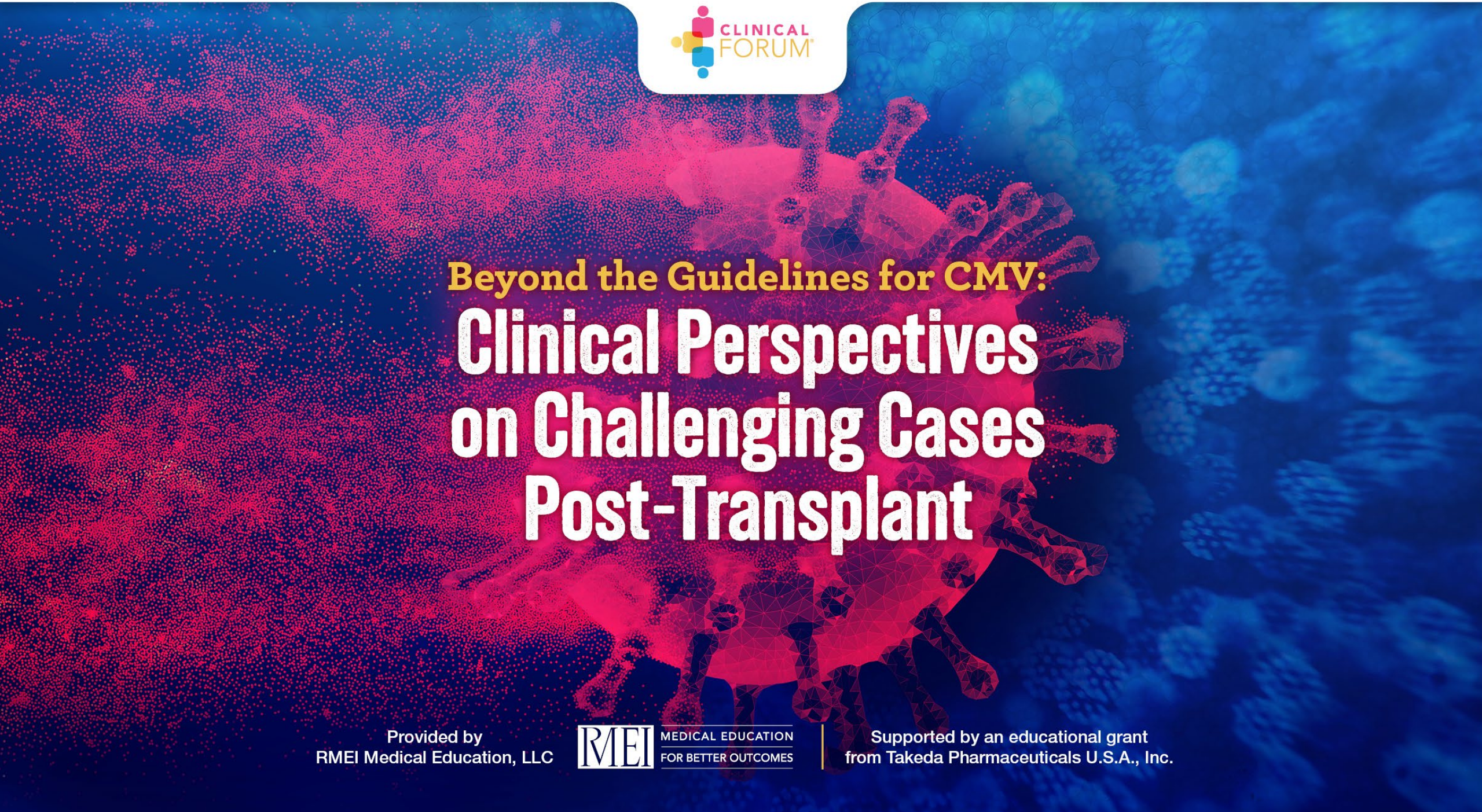
CLINICAL FORUM
Beyond the Guidelines for CMV:
Clinical Perspectives on Challenging Cases Post-Transplant
Provided by
RMEI Medical Education, LLC
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Supported by an educational grant
from Takeda Pharmaceuticals U.S.A., Inc.

Diagnosing and Treating CMV in the Post-Transplant Setting

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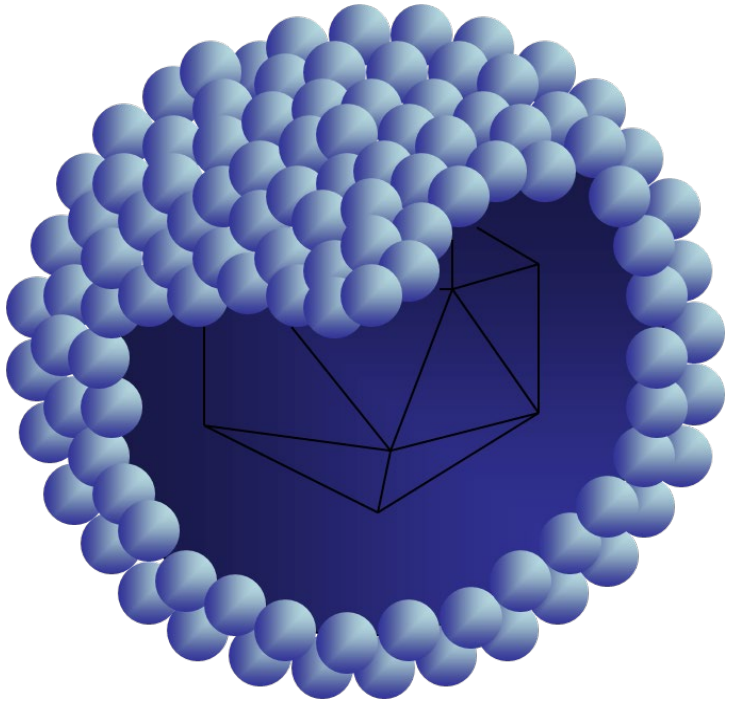
CMV Overview



Cytomegalovirus (CMV)

- Member of the beta herpesvirus group
- Frequently observed opportunistic pathogen in transplant recipients
- Establishes life-long latency after initial infection
- Sources
  - **DONOR**
  - Recipient
  - *Blood products*
  - *Community*

CMV is the Most Consequential Opportunistic Infection After Transplant

Consequence	HCT	SOT
Tissue invasive disease (GI tract, lungs, liver, CNS, retina, disseminated)	√	√
Opportunistic co-infections (viral, bacterial, fungal)	√	√
Graft impact	Increased risk of acute GvHD in T-cell depleted grafts Increased risk of chronic GvHD	Increased risk of post-transplant lymphoma Increased risk of graft rejection
Mortality	Increased non-relapse and overall mortality	Increased mortality

GvHD, graft-vs-host disease; SOT, solid organ transplant; GI, gastrointestinal; CNS, central nervous system; HCT, hematopoietic cell transplant

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931; Hakki M, et al. *Transplant Cell Ther*. 2021;27(9):707-719;
Boeckh M, et al. *Blood*. 2009;113(23):5711-5719; Ljungman P, et al. *Lancet Infect Dis*. 2019;19(8):e260-e272.

CMV in SOT and HCT: Risk Factors

SOT

- **Transplant type:** Lung and small bowel at higher risk than kidney or liver
- **Donor/recipient CMV serostatus:** D+/R- highest risk
- **Intensive immunosuppression**
- **Acute rejection** requiring intensive immunosuppression
- **Advanced age**
- **Hypogammaglobulinemia**
- **Lymphopenia**

HCT

- **Transplant type:** Mismatched or unrelated donor, cord blood, and T-cell depleted grafts at higher risk
- **Donor/recipient CMV serostatus:** D-/R+ highest risk
- **Intensive conditioning regimen**
- **GvHD:** Acute and chronic
- **Advanced age**

SOT, solid organ transplant; HCT, hematopoietic cell transplant; GvHD, graft-vs-host disease

Razonable RR, Humar A. *Clin Transplant*. 2019;33(9):e13512.
Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719.

Clinical Presentation

Asymptomatic Infection

Detection of CMV DNA in the blood without clinical signs and symptoms

CMV Syndrome

Fever, malaise, fatigue, leukopenia, thrombocytopenia, elevated ALT

+ CMV DNAemia

Tissue-invasive Disease

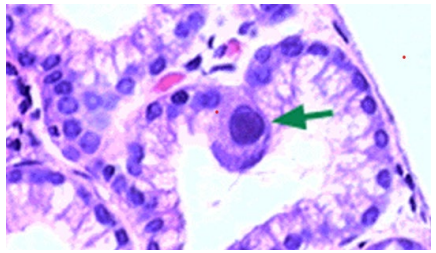
End-organ involvement: gastrointestinal disease, pneumonia, hepatitis, allograft involvement, retinitis, encephalitis

Razonable RR, et al. *Clin Transplant.* 2019;33(9):e13512.

CMV Laboratory Diagnosis of Infection

Molecular Assays (Nucleic acid amplification test)

- Detect CMV DNA
- Primary diagnostic assay used for detection of infection – substrates whole blood versus plasma
  - CMV QNAT (quantitative assay) provides assessment of "viral load"
    - Higher viral loads correlate with increased symptoms
    - Can have disease with negative viral load (especially with gastrointestinal involvement)
    - Low level DNAemia may not be clinically significant
    - Due to interlaboratory variability, important to use same lab for all testing in individual patient



Antigenemia

- pp65 antigenemia assay detects pp65 antigen in blood leukocytes
- Replaced in most centers by molecular assays

Histopathology

- Gold standard for diagnosis of end-organ CMV diseases (except retinitis)
- Invasive procedure required to obtain tissue, limits utility
- Most useful in cases where concomitant pathology (allograft rejection) or co-pathogens are suspected or low/negative DNAemia with suspicion for CMV

NAT, nucleic acid amplification; QNAT, quantitative NAT

Razonable RR, Humar A. *Clin Transplant*. 2019;33(9):e13512.

CMV Laboratory Diagnosis: Other Tests

Viral Culture (very rarely done)

- Highly specific, but poor sensitivity and slow turnaround time limits utility

CMV Serology (not recommended for diagnosis of active infection)

- Seroconversion may not occur in the setting of immunosuppression and will not identify infection in seropositive individuals
- Primarily used to determine risk status in the pretransplant setting

Immunologic Assessments

- Immune monitoring can assess nonspecific and CMV-specific T-cell quantity and/or function
  - Nonspecific tests include absolute lymphocyte count, CD4+T-cell count, and mitogen T-cell immune responses
  - CMV-specific T-cell assays include IGRA, ELISpot, ICS for interferon-gamma using flow cytometry, and MHC-multimer-based assays
    - Absence of adequate CMV-specific CD4+ and/or CD8+ T-cell immunity correlates with higher risk of CMV disease, treatment failure, and CMV relapse
    - Availability and cost can impact utilization and determination of optimal use of CMV specific T-cell assays

IGRA, interferon-gamma release assay; ELISpot, enzyme-linked immunosorbent spot; ICS, intracellular cytokine staining; MHC, major histocompatibility complex

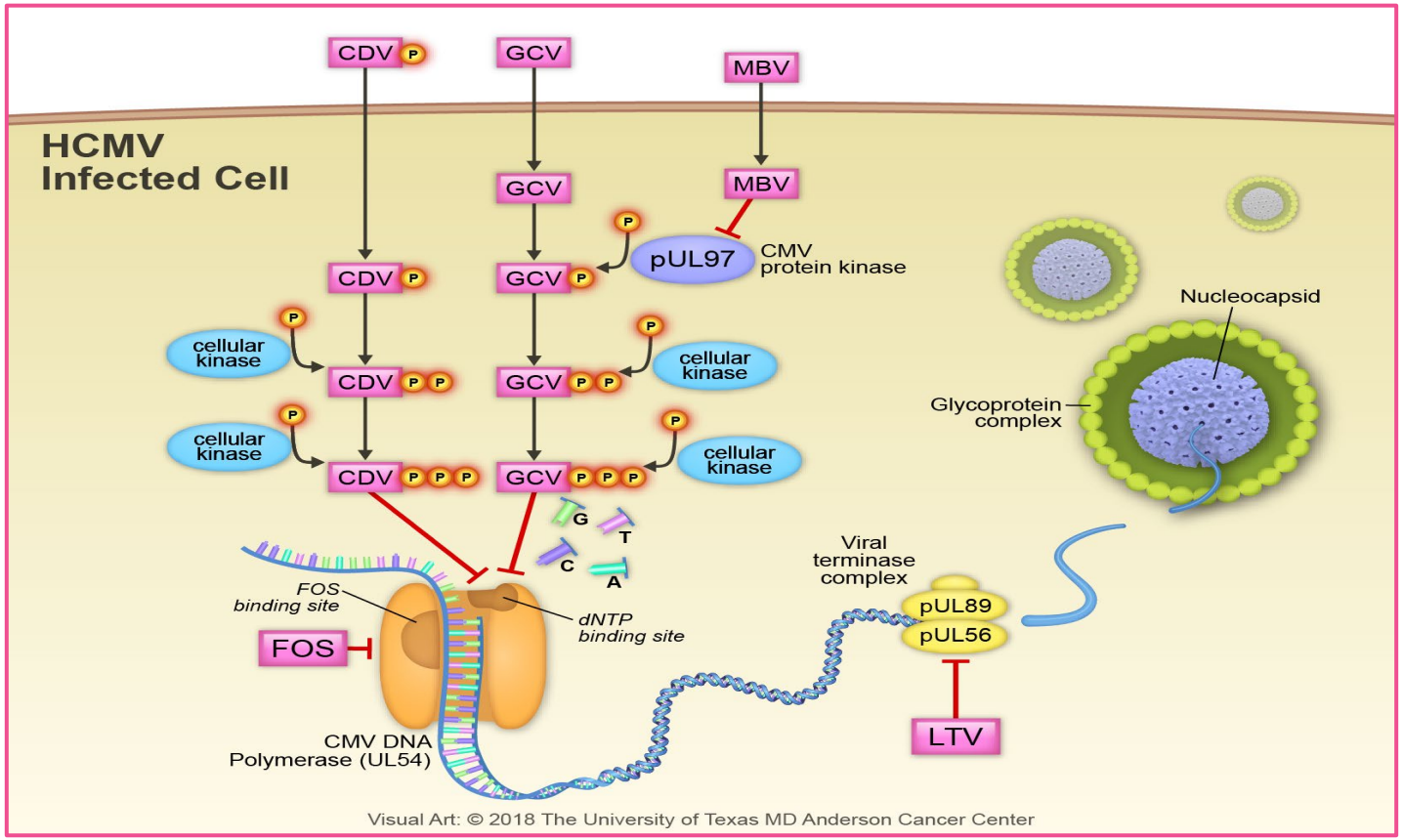
Razonable RR, Humar A. *Clin Transplant*. 2019;33(9):e13512.

Thresholds for Preemptive Treatment Have Yet to be Established

- Thresholds vary with:
  - Organ
  - Risk group (CMV donor/recipient serostatus)
  - Testing platform
  - Center/Clinic
- No single standard recommendation
- In highest risk preemptive group, some consider any quantifiable DNA level an indication for antiviral intervention
- Duration of antiviral for preemptive therapy varies
  - Should ensure that viremia has resolved

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.
Singh N, et al. *JAMA*. 2020;323(14):1378-1387.

Mechanism of Action of Antivirals



HCMV, human cytomegalovirus; CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir

Foolad F, et al. *Expert Rev Clin Pharmacol.* 2018;11(10):931-941.

CMV Antivirals

Antiviral Drugs	Route of Administration	CMV Target	Use for CMV in Transplant Patients
Ganciclovir	Intravenous	DNA polymerase (UL54)	Treatment* and prevention
Valganciclovir	Oral	UL54	Treatment* and prevention
Foscarnet	Intravenous	UL54	Treatment*
Cidofovir	Intravenous	UL54	Treatment*
Maribavir	Oral	pUL97 kinase	Treatment of post-transplant (SOT and HCT) refractory/resistant CMV infection/disease
Letermovir	Oral, intravenous	Terminase complex (UL56,51,89)	Prophylaxis in CMV seropositive HCT recipients; prophylaxis in high-risk kidney transplant recipients (Donor+/Recipient-)

*Not FDA approved for the treatment of CMV infection or disease in transplant patients
SOT, solid organ transplant; HCT, hematopoietic cell transplant

Side Effects and Toxicities

Antiviral Agent	Bone Marrow	Kidney	Unique GI*	Relevant Drug Interactions
Ganciclovir IV/valganciclovir PO	✓			MMF/MPA, TMP SMX
Foscarnet		✓		
Cidofovir		✓		
Letermovir (HCT and renal transplant approved, CMV prophylaxis only)				CNI, mTOR
Maribavir (SOT and HCT approved, refractory/resistant CMV treatment)			Altered taste	CNI, mTOR

HCT, hematopoietic cell transplant; SOT, solid organ transplant; MMF, mycophenolate mofetil; MPA, mycophenolic acid; TMP-SMZ, trimethoprim/sulfamethoxazole; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin

*All medications have been described to cause nausea and vomiting, and all but cidofovir have been associated with diarrhea

Managing CMV Antiviral Side Effects in SOT

Leukopenia/Neutropenia (VGCV/GCV)

- Reduce or stop MMF and/or stop VGCV/GCV
- Stop TMP-SMZ and other medications associated with cytopenias
- For (val)ganciclovir, do not dose reduce for low WBC, always dose to GFR
  - Increases risk of resistance (especially with infection)
  - Support WBC with growth factors (G-CSF), *or*
    - **If prevention:** Switch to preemptive monitoring with weekly blood checks or to letermovir

      (±HSV/VZV prophylaxis if letermovir switch)
    - **If treatment:** Switch to foscarnet or maribavir

Nephrotoxicity

- Maintain adequate hydration
- Avoid concomitant use of other nephrotoxic drugs
- **Ensure GFR appropriate dosing**
- Consider alternate therapies if appropriate

MMF, mycophenolate mofetil; VGCV, valganciclovir; GCV, ganciclovir; TMP-SMZ, trimethoprim/sulfamethoxazole; WBC, white blood cell; GFR, glomerular filtration rate; G-CSF, granulocyte colony stimulating factor; HSV, herpes simplex virus; VZV, varicella-zoster virus;

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.
Khawaja F, et al. *Clin Microbiol Infect*. 2023;29(1):44-50.

Panel Discussion

- How do you determine when to treat a patient with a rising viral load?

Conquering Refractory and Drug-Resistant CMV

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Refractory and Resistant CMV

Refractory*	Resistant
• Increasing or persistent viral load after at least 2 weeks of adequate antiviral therapy • Worsening or failure to improve signs and symptoms after at least 2 weeks of adequate antiviral therapy	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs

*Not all patients with refractory CMV have resistant virus.

CMV, cytomegalovirus

Chemaly RF, et al. *Clin Infect Dis*. 2019;68(8):1420-1426; Yong MK, et al. *Transplant Cell Ther.* 2021;27(12):957-967.

Comparison of Outcomes in SOT Patients With Ganciclovir-Resistant versus Ganciclovir-Sensitive CMV

Outcome	Cases (n = 37)	Controls (n = 109)	*P* Value
Morbidity measures			
Days to clearance of viremia, median (IQR)	113 (50–394)	53 (32–149)	.006
≥20% decrease in eGFR by 3 mo after CMV diagnosis	15 (41.7)	21 (19.4)	.008
Well days[a] in the 3 mo after CMV diagnosis, mean (SE)	72.7 (4.8)	81.0 (1.7)	.039
Rejection within 1 y following CMV diagnosis			
All organs	15 (40.5)	38 (34.9)	.54
Kidney	4 (66.7)	2 (10.5)	.005
Mortality			
3 mo	4 (10.8)	1 (0.92)	.004[b]
12 mo	6 (16.2)	6 (5.5)	.032

[a] Alive and non-hospitalized; [b] Fisher exact test

Drug resistant CMV correlates with increased morbidity and mortality

CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SE, standard error

Fisher CE, et al. *Clin Infect Dis.* 2017;65(1):57-63.

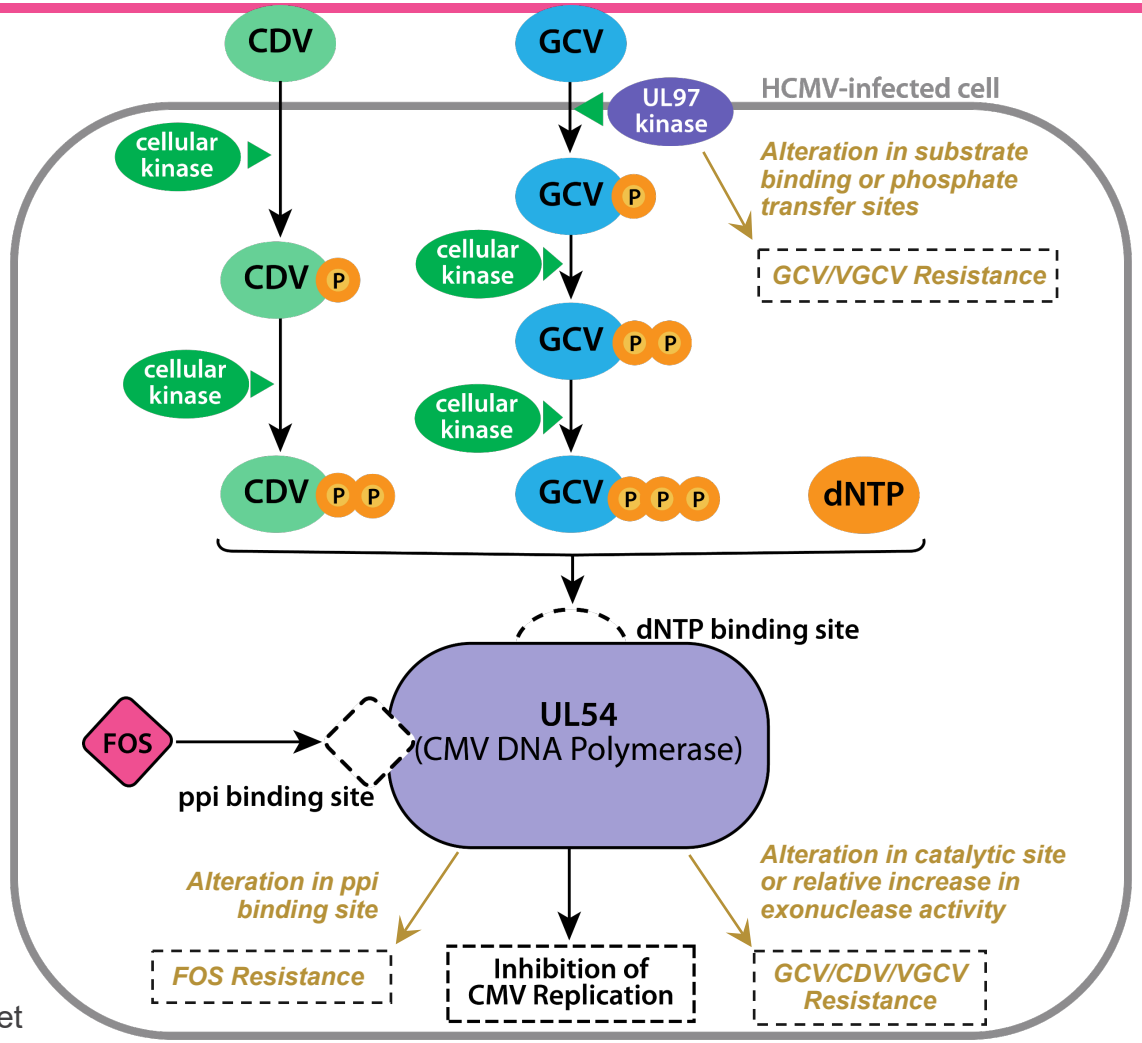
Risk Factors for Resistant and Refractory CMV

SOT Specific	HCT Specific	Both
• CMV D+/R- status • Intestinal/multivisceral organ and lung transplant recipients • Allograft rejection	• CMV R+ status • HLA mismatch • Haploidentical and T-cell depleted HCT • Cord blood HCT • Lack of immune reconstitution • GvHD	• Lymphopenia • Type and potency of immunosuppressive therapy (eg, T-cell depleting agents, belatacept) • Reduced CMV-specific immunity • Cumulative exposure to anti-CMV therapy >4 weeks • Inappropriately low antiviral dose

SOT, solid organ transplant; HCT, hematopoietic cell transplant, GvHD; graft-vs-host disease

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.
Yong MK, et al. *Transplant Cell Ther.* 2021;27(12):957-967.
Hakki M, et al. *Transplant Cell Ther.* 2021;27(9):707-719.

Mechanism of Action of Antiviral Drugs for CMV



GCV, ganciclovir; CDV, cidofovir; FOS, foscarnet

El Chaer F, et al. *Blood*. 2016;128(23):2624-2636.

Antiviral Resistance Testing

When to Test

- Antiviral drug resistance should be suspected when there is treatment-refractory CMV infection
- For GCV, cumulative exposure of at least 4 or more weeks
  - Including longer than 2 weeks of continuous full and appropriately-dosed therapy

How to Test

- Genotypic assays for viral drug resistance mutations in UL97 and UL54 genes
  - 7 most common ("canonical") UL97 mutations – 80% cases
  - Several UL54 mutations

7 Canonical GCV-Resistant UL97 Kinase Mutations*

M460V/I	H520Q
C592G	A594V
L595S	C603W

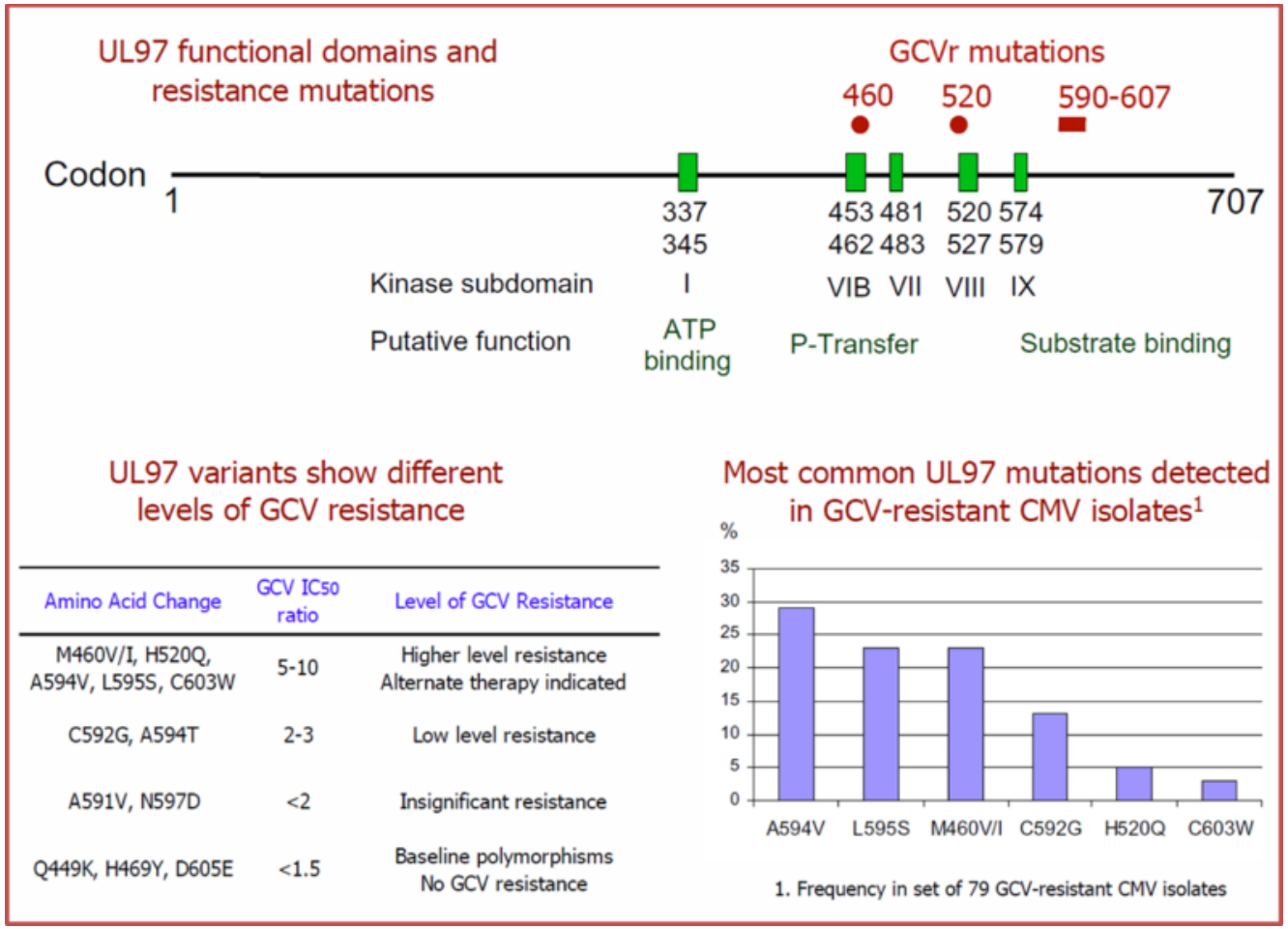
*Initially detected in >80% of cases of GCV resistance in clinical practice.

GCV, ganciclovir

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.
Chou S, et al. *J Clin Microbiol.* 2017;55(7):2098-2104.

How Do You Confirm Resistant CMV?

- **Genotypic resistance testing** involves sequencing of relevant portions of the CMV genome and is the preferred method
- **Phenotypic resistance testing** involves culturing the virus in the presence of different drug concentrations and is more labor intensive



Courtesy of S. Chou

Lurain NS, Chou S. *Clin Microbiol Rev.* 2010;23(4):689-712.
Chou S. *Curr Opin Infect Dis.* 2015;28(4):293-299.

Treatment of Drug-Resistant/Refractory CMV

- First step is to reduce immunosuppressive therapy to the lowest feasible amount

- Therapies:
  - High-dose ganciclovir
  - Foscarnet
  - Maribavir
  - Cidofovir

- Adjunctive
  - CMV-Ig
- Investigational
  - T-cell therapy
- Off-label
  - Letermovir
  - Leflunomide
  - Artesunate
  - mTOR inhibitors (sirolimus, everolimus)

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.

High-Dose Ganciclovir

Appropriate Candidates

Best for those with:

- Low-level resistance UL97 gene mutations (C592G)
- Low-level DNAemia
- Asymptomatic or mildly symptomatic disease

Limitations

Data in SOT limited to few case series:

- 21% clearance rate in 14 patients with genotypic resistance and high-level DNAemia
- Narrow applicability

Regimen

Dose escalation from 7.5 to 10 mg/kg every 12 hours in normal renal function

Adverse Events

Neutropenia reported in approximately 50% of patients

SOT, solid organ transplant

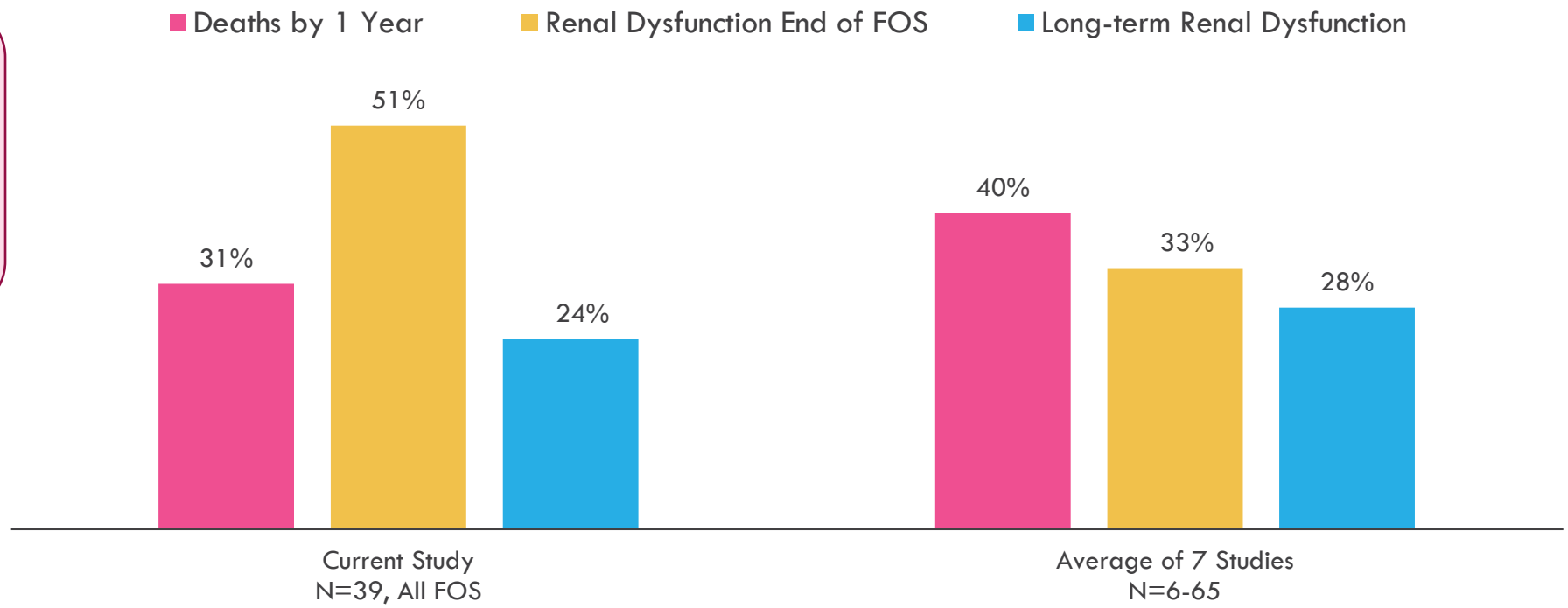
Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

Foscarnet

Studies Published After the Year 2000, Reporting Outcomes of 6 or More Transplant Recipients Treated with Foscarnet for Established CMV Infection

Overall

- Virologic clearance: 66%
- CMV relapse: 31%
- Renal dysfunction: 51%
- 1 year mortality: 31%



Limitations:
Metabolic and renal toxicity

Avery RK, et al. *Transplantation.* 2016;100(10):e74-80.

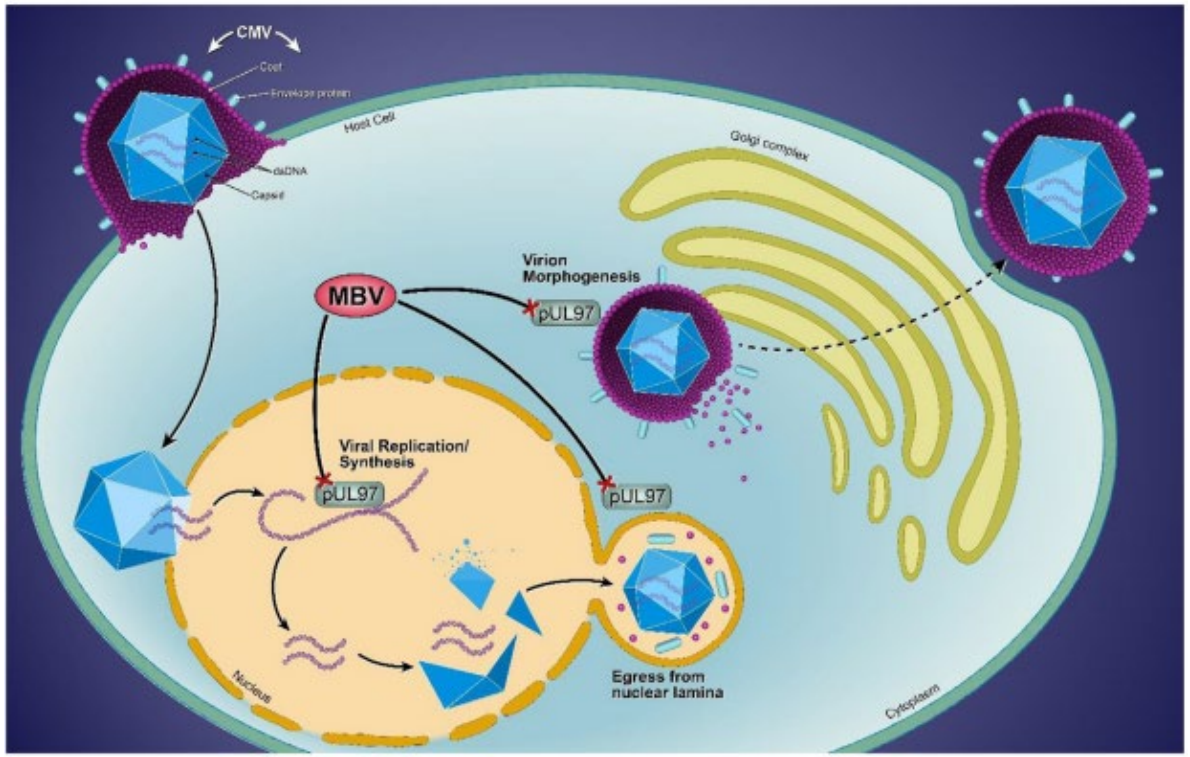
Maribavir

Mechanism of Action

- Inhibits UL97 viral protein kinase
  - Inhibits viral encapsidation
  - Inhibits nuclear egress of viral particles
- Maribavir does not affect the UL54 CMV DNA polymerase

Use

- Approved for the treatment of post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet
- Orally bioavailable
- Not myelosuppressive or nephrotoxic – main side effect is taste disturbance
- Should not be used in combination with ganciclovir or valganciclovir
- Should not be used in case of encephalitis or retinitis
- CYP3A4 inhibitor, tacrolimus dose may need to be lowered



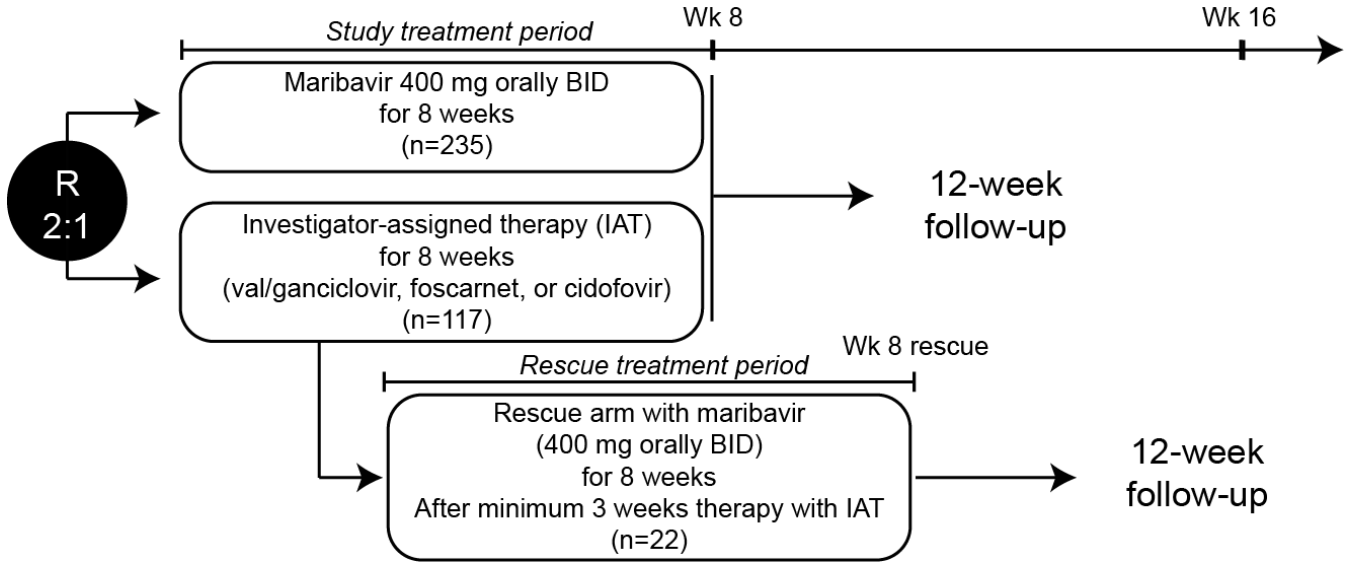
Khawaja F, et al. *Clin Microbiol Infect*. 2023;29(1):44-50.

Sun K, et al. *Clin Transl Sci*. 2024;17(1):e13696.

Maribavir Phase 3 SOLSTICE Trial: Study Design

Key Study Inclusion Criteria

- SOT/HCT recipients
- CMV infection (plasma CMV DNA ≥910 IU/mL)
- Refractory to most recent therapy (failure to achieve >1 $\log_{10}$ decrease in CMV DNA after 14 days)



End Points

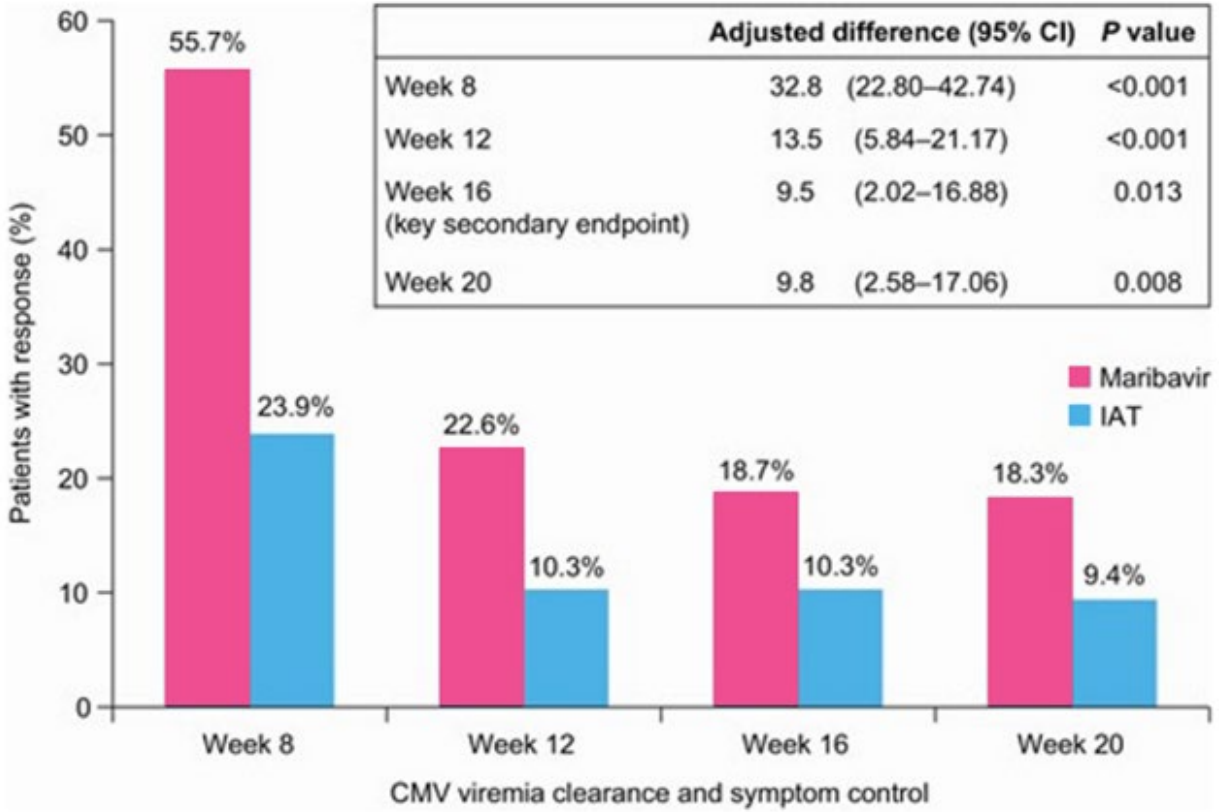
Primary	Key Secondary	Other Secondary
Confirmed CMV viremia clearance (plasma CMV DNA <LLOQ in 2 consecutive tests ≥5 days apart at central laboratory) at end of Week 8	Composite of CMV viremia clearance and symptom control at end of Week 8 and maintained through Week 16	Assess the efficacy (including symptom control) and safety of maribavir as rescue treatment

SOT, solid organ transplant; HCT, hematopoietic cell transplant; BID, twice daily; LLOQ, lower limit of quantification

Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-701.

Maribavir Phase 3 SOLSTICE Trial: Results

Confirmed Viremia Clearance and Symptom Control



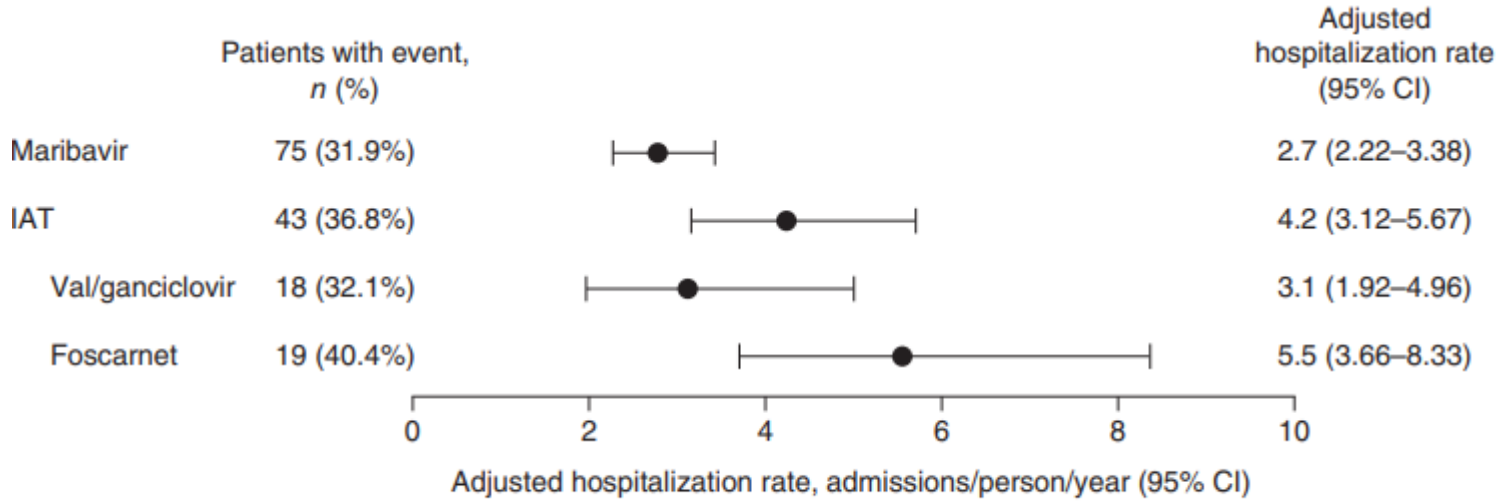
	Adjusted difference (95% CI)	*P* value
Week 8	32.8 (22.80–42.74)	<0.001
Week 12	13.5 (5.84–21.17)	<0.001
Week 16 (key secondary endpoint)	9.5 (2.02–16.88)	0.013
Week 20	9.8 (2.58–17.06)	0.008

- Maribavir was superior to IAT for CMV viremia clearance
- Viremia clearance and symptom control were better through week 20 with maribavir

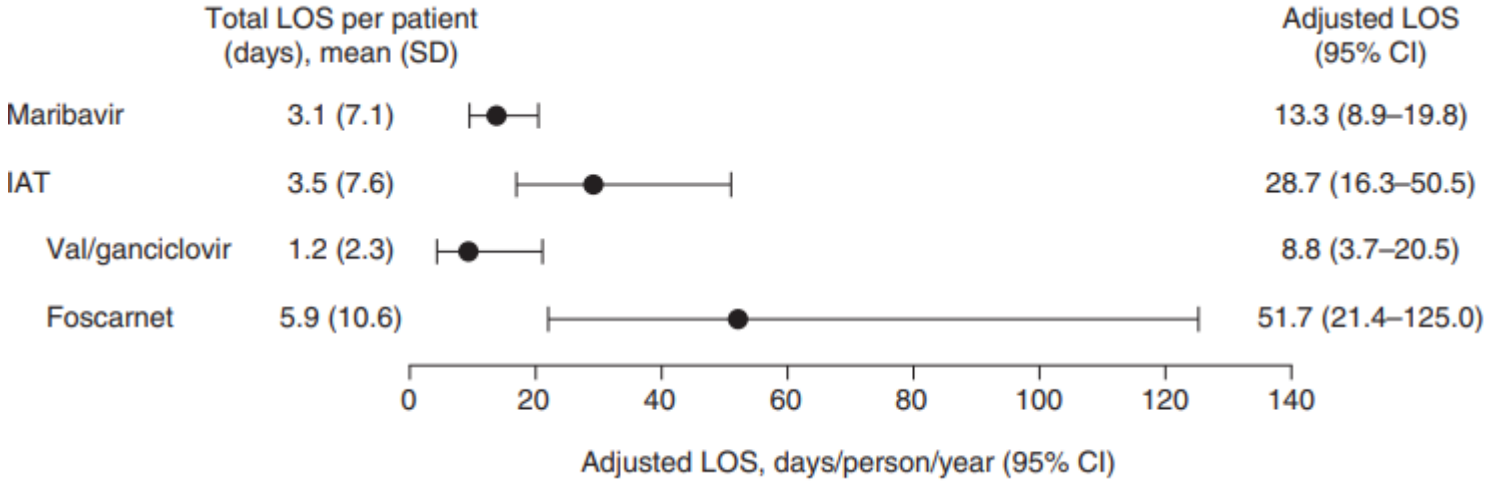
Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-701.

Maribavir Phase 3 SOLSTICE Trial: Hospitalization Rate and Length of Stay

- The adjusted annualized hospitalization rate was 34.8% lower in the maribavir arm (2.7 admissions/person/year) compared with the IAT arm (4.2 admissions/person/year) during the treatment phase (*P*=.021).



- The adjusted LOS was 53.8% less in the maribavir arm (13.3 days/person/year) compared with the IAT arm (28.7 days/person/year) during the treatment phase (*P*=.029).



IAT, investigator assigned therapy; LOS, length of stay

Hirji I, et al. *Transpl Infect Dis*. 2023;25:e14064.

Maribavir Phase 3 SOLSTICE Trial:
Treatment Emergent Maribavir Drug Resistance Mutations

- Post-treatment, emergent maribavir resistance mutations were detected in 60 (26%) of those randomized to maribavir, first detected 26 to 130 (median 56) days after starting
- All emergent maribavir resistance was attributable to 6 UL97 mutations

rMed	Gene	Amino Acid Substitution	n	Fold Increase Maribavir EC_{50}
IAT[a]	*UL97*	T409M	4	78–90
IAT[a]	*UL97*	H411L	1	69
IAT[a]	*UL97*	H411Y	2	12–18
Maribavir	*UL97*	F342Y[b]	3	4.5
Maribavir	*UL97*	T409M	30	78–90
Maribavir	*UL97*	H411L	1	69
Maribavir	*UL97*	H411N	3	9
Maribavir	*UL97*	H411Y	24	12–18
Maribavir	*UL97*	C480F[c]	21	224

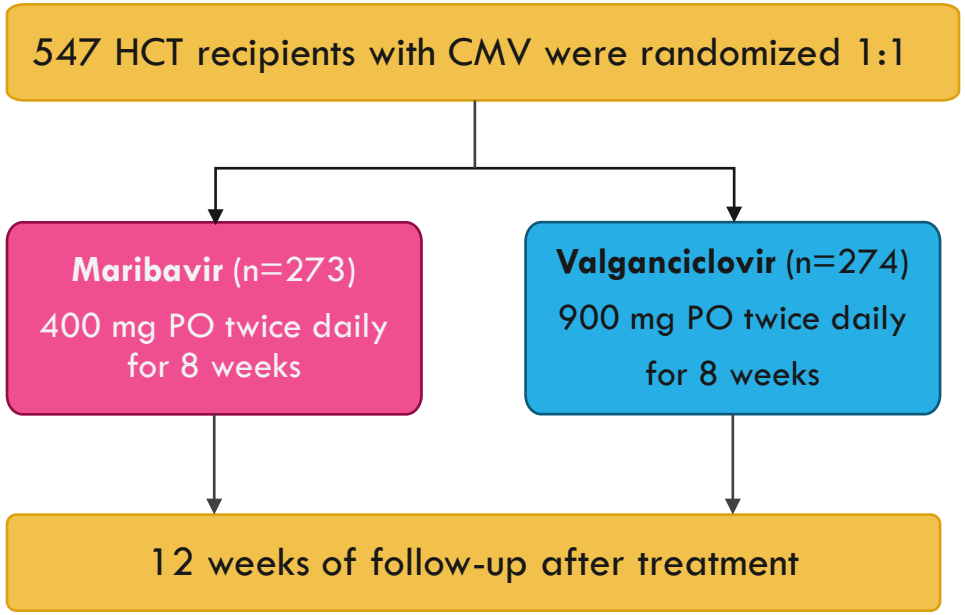
[a]Genotyped after receiving maribavir rescue
[b] Also has 6-fold increased ganciclovir EC_{50}
[c] Also has 2.3-fold increased ganciclovir EC_{50}

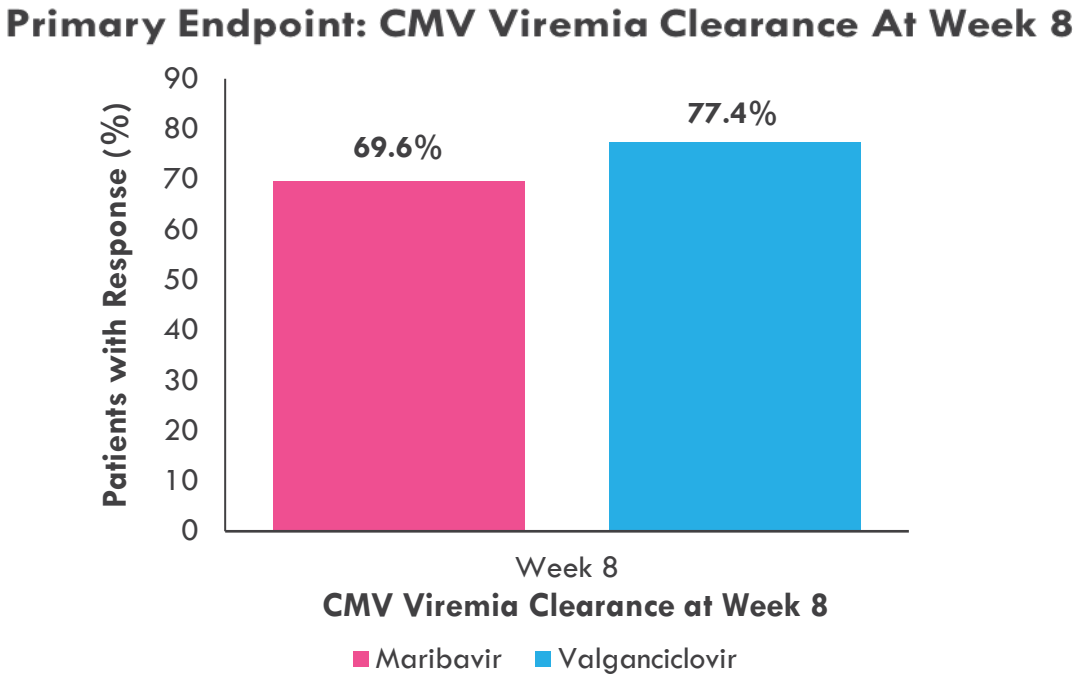
- ✓ Baseline maribavir resistance was rare [*UL27* L193F (n=1) and *UL97* F342Y (n=3)]
- ✓ Drug resistance to standard cytomegalovirus antivirals did not preclude treatment response to maribavir
- ✓ Rebound in plasma CMV DNA while on maribavir strongly suggests emerging drug resistance

DRM, drug resistance mutation

Chou S, et al. *J Infect Dis.* 2024;229(2):413-421.

Phase 3 AURORA Trial for Maribavir Preemptive Treatment of CMV in HCT





- Maribavir did not meet its primary endpoint of non-inferiority versus valganciclovir based on a prespecified non-inferiority margin of 7% (maribavir 69.6% versus valganciclovir 77.4%; adjusted difference, -7.7%; 95% CI: -14.98, -0.36)

HCT, hematopoietic cell transplant

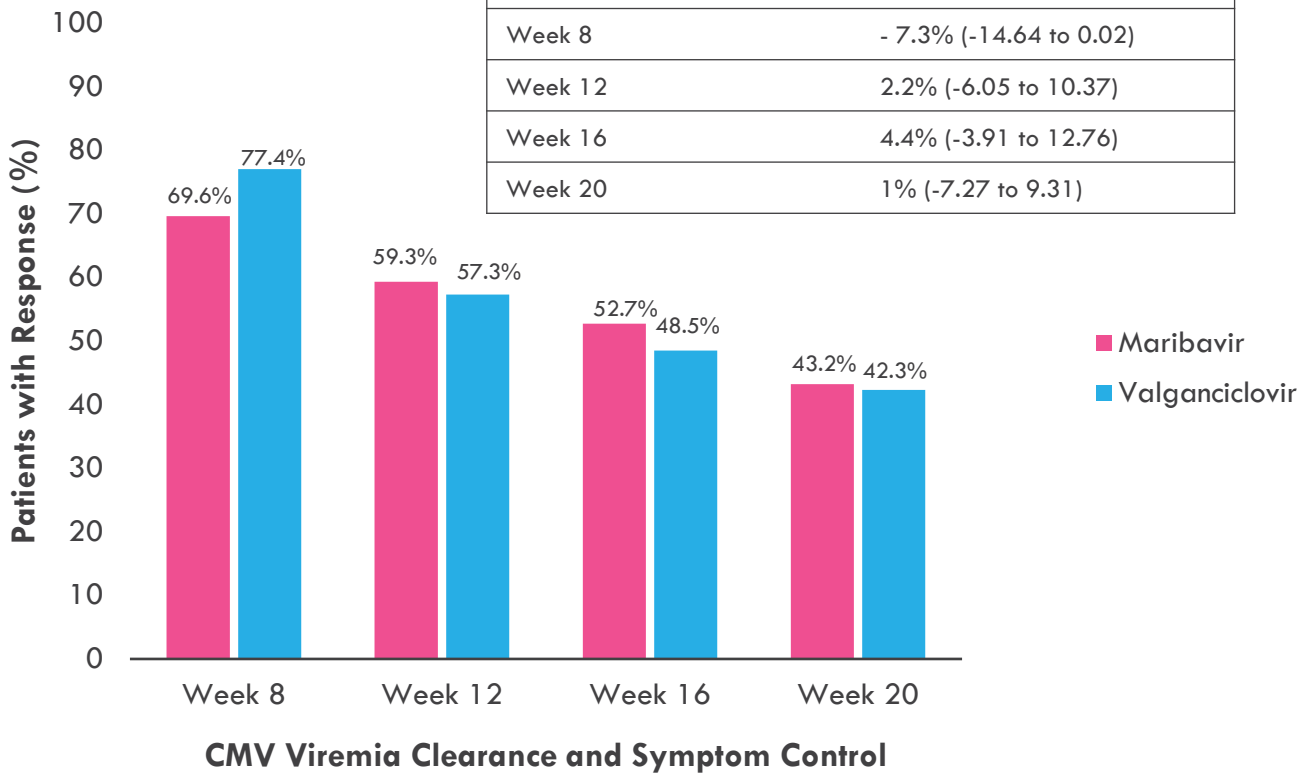
Papanicolaou GA, et al. *Clin Infect Dis*. 2024;78(3):562-572.

Phase 3 AURORA Trial for Maribavir Preemptive Treatment of CMV in HCT *(cont'd)*

- A sustained maintenance effect was observed with maribavir during post-treatment evaluations at week 12 and week 20.
- Reaffirmed maribavir's favorable safety profile compared to valganciclovir.
  - Treatment-emergent neutropenia was 21.2% for maribavir vs 63.5% for valganciclovir.
  - Rate of premature discontinuation of therapy due to neutropenia was 4% for maribavir vs 17.5% for valganciclovir.

Secondary Endpoint: Confirmed Viremia Clearance and Symptom Control

	Adjusted difference (95% CI)
Week 8	- 7.3% (-14.64 to 0.02)
Week 12	2.2% (-6.05 to 10.37)
Week 16	4.4% (-3.91 to 12.76)
Week 20	1% (-7.27 to 9.31)



HCT, hematopoietic cell transplant

Papanicolaou GA, et al. *Clin Infect Dis*. 2024;78(3):562-572.

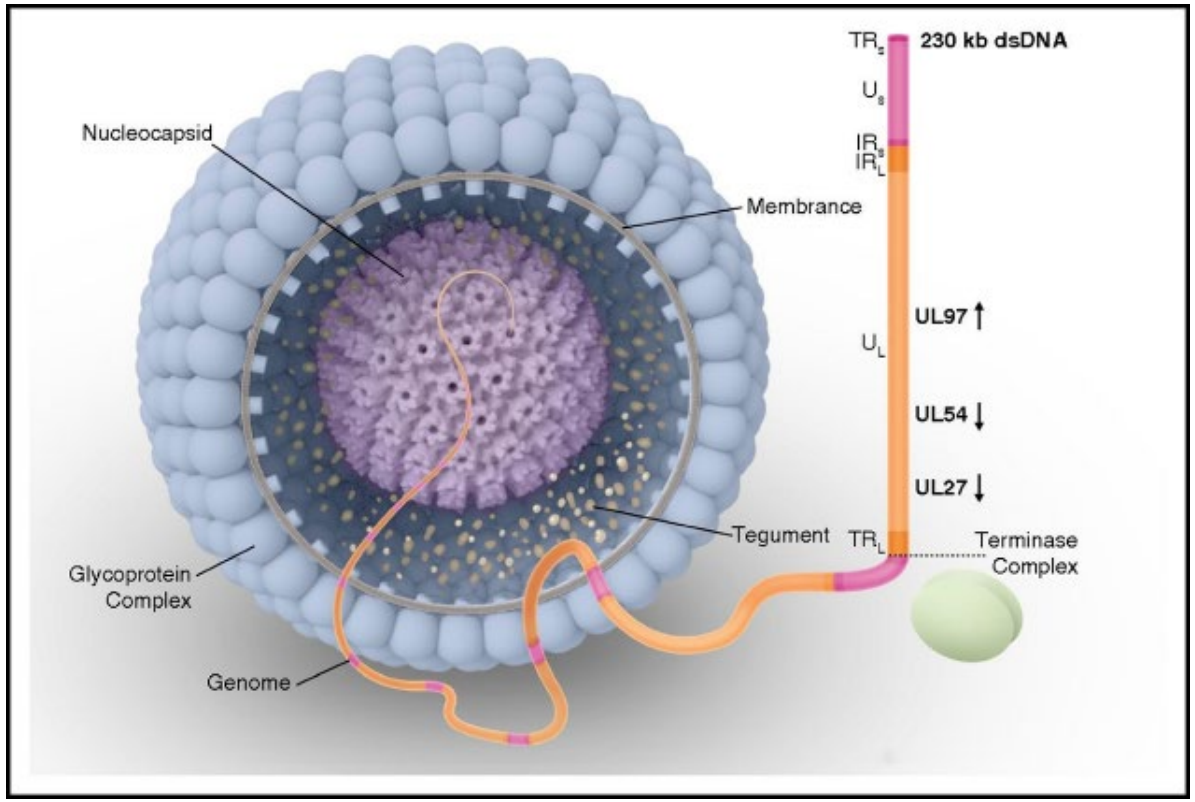
Letermovir

Mechanism of Action

- CMV replication involves cleaving of concatemeric genomic DNA and packaging of each genome into preformed virus capsids by the CMV terminase complex (UL56, UL89)
- Letermovir inhibits the terminase complex by binding to UL56

Use

- Approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HCT
- Approved for prophylaxis in high-risk kidney transplant recipients (Donor+/Recipient-)
- Not myelosuppressive or nephrotoxic
- CYP3A4 inhibitor, tacrolimus dose may need to be lowered



El Chaer F, et al. *Blood*. 2016;128(23):2624-2636.

Letermovir Treatment for R/R CMV Infection

- Limited clinical studies with R/R CMV infection – off-label, unproven indication
  - Multicenter study of 47 SOT and HCT patients with CMV treated with letermovir[1]
    - 37 patients with low viral load (<1000 IU/mL) had good response
    - Only 2 patients had viral load increase >1 log by 12 weeks
    - 10 patients with higher viral load had mixed response (~60% response to <1000 IU/mL)
  - Study of 28 lung transplant patients with R/R CMV treated with letermovir[2]
    - 14 patients with viral load >10,000 IU/mL
    - 82.1% response with viral load decline >1$\log_{10}$
    - 3 patients developed letermovir resistance mutations (UL56, C325Y)
- Uncertainty about optimal dosing[3] and possible low barrier to resistance[4,5]
- Insufficient data to recommend use of letermovir monotherapy for treatment. Proceed with caution.

R/R, refractory/resistant; SOT, solid organ transplant; HCT, hematopoietic cell transplant

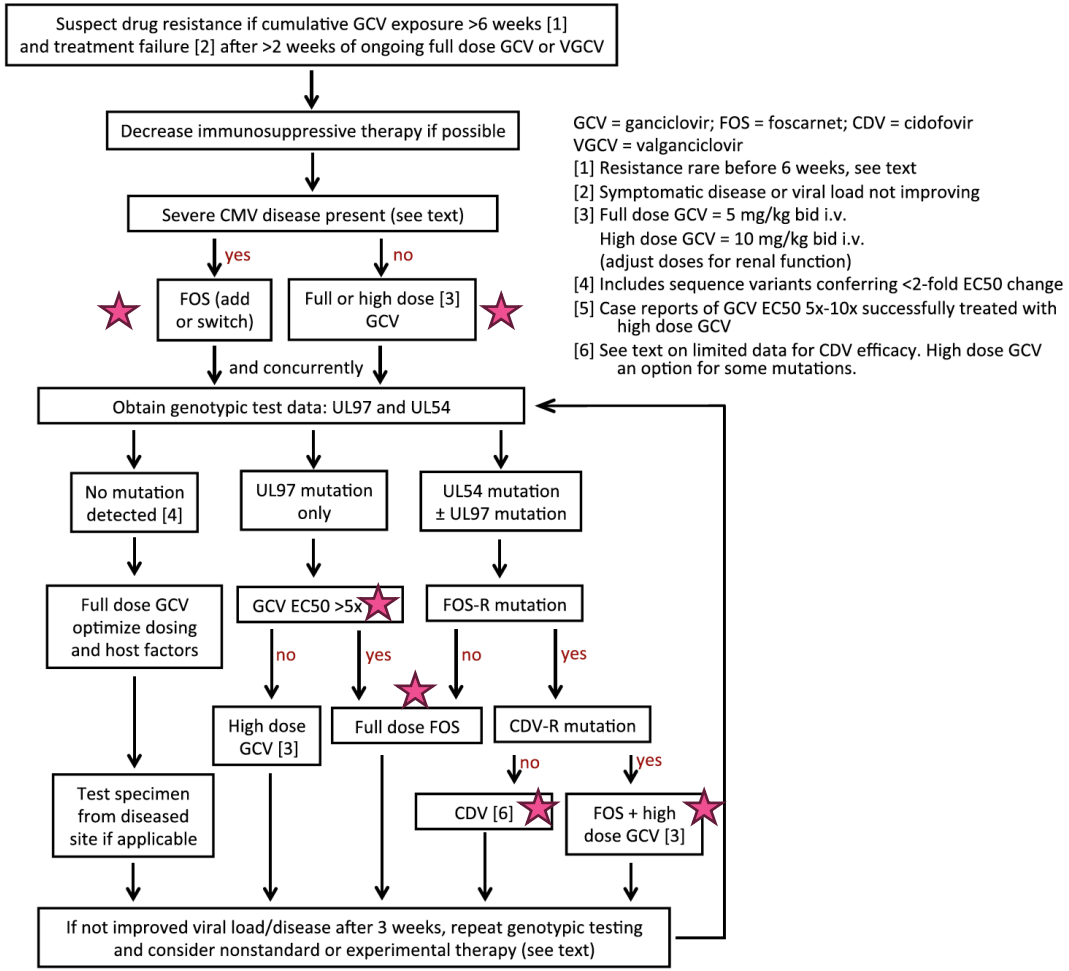
1. Linder KA, et al. *Transpl Infect Dis.* 2021;23(4):e13687.
2. Veit T, et al. *Am J Transplant.* 2021;21(10):3449-3455.
3. Hakki M. *Curr Hematol Malig Rep.* 2020;15(2):90-102.
4. Shigle TL, et al. *Ther Adv Hematol.* 2020;11:2040620720937150.
5. Chou S, et al. 2015;59(10):6588-6593.

Other Adjunctive, Investigational, and Off-label Therapies

- CMV-Ig or IVIG
  - Adjunctive use in severe disease
  - Supply and cost limitations
- Adoptive T-cell therapy
  - Good safety profile
  - Mixed rates of response
  - Logistical and cost limitations
  - Experimental: clinical studies in SOT recipients ongoing
- mTOR inhibitors as part of immunosuppressive regimen
  - Reduces risk of CMV infection
  - Tolerability an issue
- Leflunomide and Artesunate
  - Mixed outcomes in very limited data
  - Generally, not recommended

Kotton C, et al. *Transplantation* 2018;102(6):900–931.
Smith C, et al. *Clin Infect Dis.* 2019;68(4):632-640.
Demopoulos L, et al. *Transplant Proc.* 2008;40(5):1407-1410.

Algorithm for Management of R/R CMV



GCV = ganciclovir; FOS = foscarnet; CDV = cidofovir
VGCV = valganciclovir
[1] Resistance rare before 6 weeks, see text
[2] Symptomatic disease or viral load not improving
[3] Full dose GCV = 5 mg/kg bid i.v.
High dose GCV = 10 mg/kg bid i.v.
(adjust doses for renal function)
[4] Includes sequence variants conferring <2-fold EC50 change
[5] Case reports of GCV EC50 5x-10x successfully treated with high dose GCV
[6] See text on limited data for CDV efficacy. High dose GCV an option for some mutations.

Kotton C, et al. *Transplantation* 2018;102(6):900-931.

★ Indicates potential changes in updated guidelines

Panel Discussion

- How do you approach a patient with suspected refractory CMV disease?
- Do you use CMV-Ig?

Case Challenges in Difficult-to-Treat CMV After Transplant

Renal Transplant Patient with Resistant CMV

Patient Case 1: 57-year-old male renal transplant patient

History

- Diabetes mellitus type 2, hypertension, end-stage renal disease
- Underwent deceased donor renal transplant
  - CMV D+/R-
  - Induction immunosuppression with anti-thymocyte globulin
  - Maintenance immunosuppression with mycophenolate and tacrolimus
  - Prophylaxis with 6 months of valganciclovir and 12 months of trimethoprim/sulfamethoxazole

What Happened Next?

- 18 months after transplant presented with chills, weakness x10 days
  - Febrile to 38.6°C, other vitals stable
  - Exam unremarkable
  - WBC 1.6 cells/µL (16% atypical lymphocytes), platelets 90,000 cells/µL
  - CMV PCR $\log_{10}$ 4.23 (17,000) IU/mL

Renal Transplant Patient with Resistant CMV *(cont'd)*

Patient Case 1: 57-year-old male renal transplant patient

- Initiated on valganciclovir treatment dose 900 mg po twice daily
- Week 1
  - Symptoms improved
  - PCR down to $\log_{10}$ 3.84 (7,000) IU/mL
- Week 3
  - PCR $\log_{10}$ 3.69 (5,000) IU/mL
- Week 6
  - PCR back to $\log_{10}$ 4.07 (12,000) IU/mL
  - Still feeling well

Renal Transplant Patient with Resistant CMV *(cont'd)*

Patient Case 1: 57-year-old male renal transplant patient

- Resistance testing obtained:

Ganciclovir UL54 Gene Target	None Detected	[None Detected]	Final
Ganciclovir UL97 Gene Target	Resistant at Site H520Q	[None Detected]	Final
Foscarnet UL54 Gene Target	None Detected	[None Detected]	Final
Cidofovir UL54 Gene Target	None Detected	[None Detected]	Final
Letermovir UL56	None Detected	[None Detected]	Final

- eGFR 35 mL/min/1.73 m^2
- WBC <2000 cells/µL
- Kidney transplant team asking for therapeutic guidance
- Patient asking for least toxic option

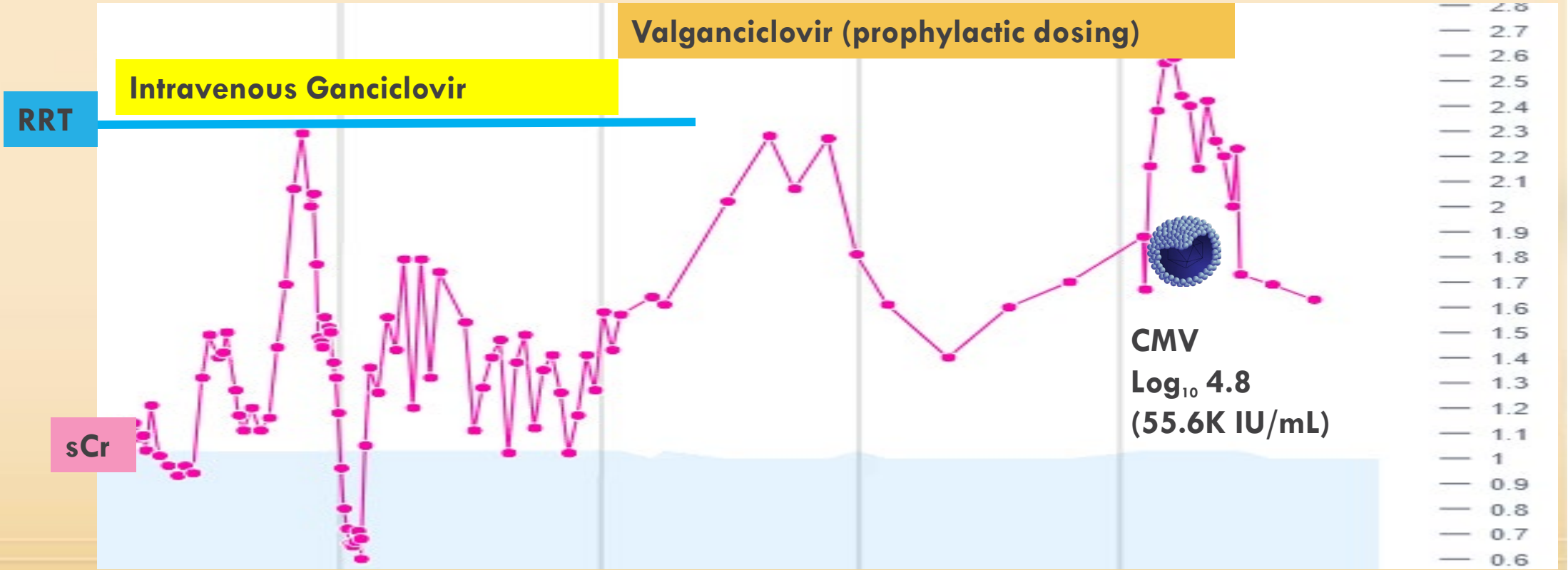
Renal Transplant Patient with Resistant CMV *(cont'd)*

Patient Case 1: 57-year-old male renal transplant patient

- Initiated on maribavir 400 mg po twice daily
- CMV PCR steadily declined
- WBC and eGFR remained unchanged
- CMV PCR <35 IU/mL by week 5 of maribavir treatment

Liver Transplant Patient: Suspicion for Resistance

Patient Case 2: 64-year-old female
CMV D+/R-, underwent liver transplant for MASH, c/b AKI



Liver Transplant Patient: Suspicion for Resistance *(cont'd)*

Patient Case 2: 64-year-old female
CMV D+/R-, underwent liver transplant for MASH, c/b AKI

- High suspicion for ganciclovir resistance
  - Prolonged GCV/VGCV exposure
  - Varying renal function increased potential for underdosing
  - High level of CMV DNAemia while taking VGCV (documented adherence)

Ganciclovir,GCV	Resistant
Foscarnet,FOS	Sensitive
Cidofovir,CDV	Resistant
Maribavir,MBV	Sensitive
Letermovir,LTV	Sensitive

Liver Transplant Patient: Suspicion for Resistance *(cont'd)*

Patient Case 2: 64-year-old female
CMV D+/R-, underwent liver transplant for MASH, c/b AKI

- Given concerns for resistance, maribavir ordered initially for CMV treatment
  - Concerns affecting this decision
    - Higher viral load (>Log_{10} 4.5) - ???
    - Drug interaction with tacrolimus
    - Taste disturbance
    - Insurance coverage
- Following insurance approval, initiated maribavir as an inpatient
- Patient tolerated maribavir well
- Drug interactions manageable
- Responded to treatment with resolution of infection

Heart Transplant Patient with Multi-Resistant CMV

Patient Case 3: 64-year-old male heart transplant patient

History

- Diabetes mellitus type 2, hypertension, coronary artery disease with ischemic cardiomyopathy
- Underwent heart transplant in 6/2022, no post-operative complications
  - CMV D+/R-
  - Induction with basiliximab
  - Maintenance immunosuppression with tacrolimus, mycophenolate and prednisone
  - Prophylaxis with 6 months of valganciclovir and 12 months of trimethoprim/sulfamethoxazole
  - Course complicated by leukopenia and CKD (eGFR 40 mL/min/1.73 m^2)

What Happened Next?

- On 1/25/2024 CMV PCR detected at Log_{10} 3.22 (1,660) IU/mL
- Started on valganciclovir 450 mg po twice daily

Heart Transplant Patient with Multi-Resistant CMV *(cont'd)*

Patient Case 3: 64-year-old male heart transplant patient

- 2/5/2024 CMV PCR Log_{10} 2.52 (337) IU/mL
- 2/25/2024 CMV PCR Log_{10} 2.82 (676) IU/mL
- Patient asymptomatic, continued on valganciclovir
- 3/10/2024 CMV PCR Log_{10} 4.66 (45,800) IU/mL

- CMV resistance testing results on 3/17/2024
  - Mutations at both UL97 and UL54

Ganciclovir UL54 Gene Target	Resistant at Site N408K	[None Detected]	Final
Ganciclovir UL97 Gene Target	Resistant at Site M460I	[None Detected]	Final
Foscarnet UL54 Gene Target	None Detected	[None Detected]	Final
Cidofovir UL54 Gene Target	Resistant at Site N408K	[None Detected]	Final
Letermovir UL56	None Detected	[None Detected]	Final
Maribavir UL97	None Detected	[None Detected]	Final

Heart Transplant Patient with Multi-Resistant CMV *(cont'd)*

Patient Case 3: 64-year-old male heart transplant patient

- Patient hospitalized for monitoring and therapy
- On admission:
  - WBC 1.13 cells/µL
  - sCr 1.5 mg/dL (eGFR 40 mL/min/1.73 m^2)
  - CMV PCR log_{10} 5.23 (168,000) IU/mL
- Started on foscarnet 60 mg/kg q24 hrs
  - Intense monitoring and hydration
- CMV PCR peaked at Log_{10} 5.90 (790,000) IU/mL

Heart Transplant Patient with Multi-Resistant CMV *(cont'd)*

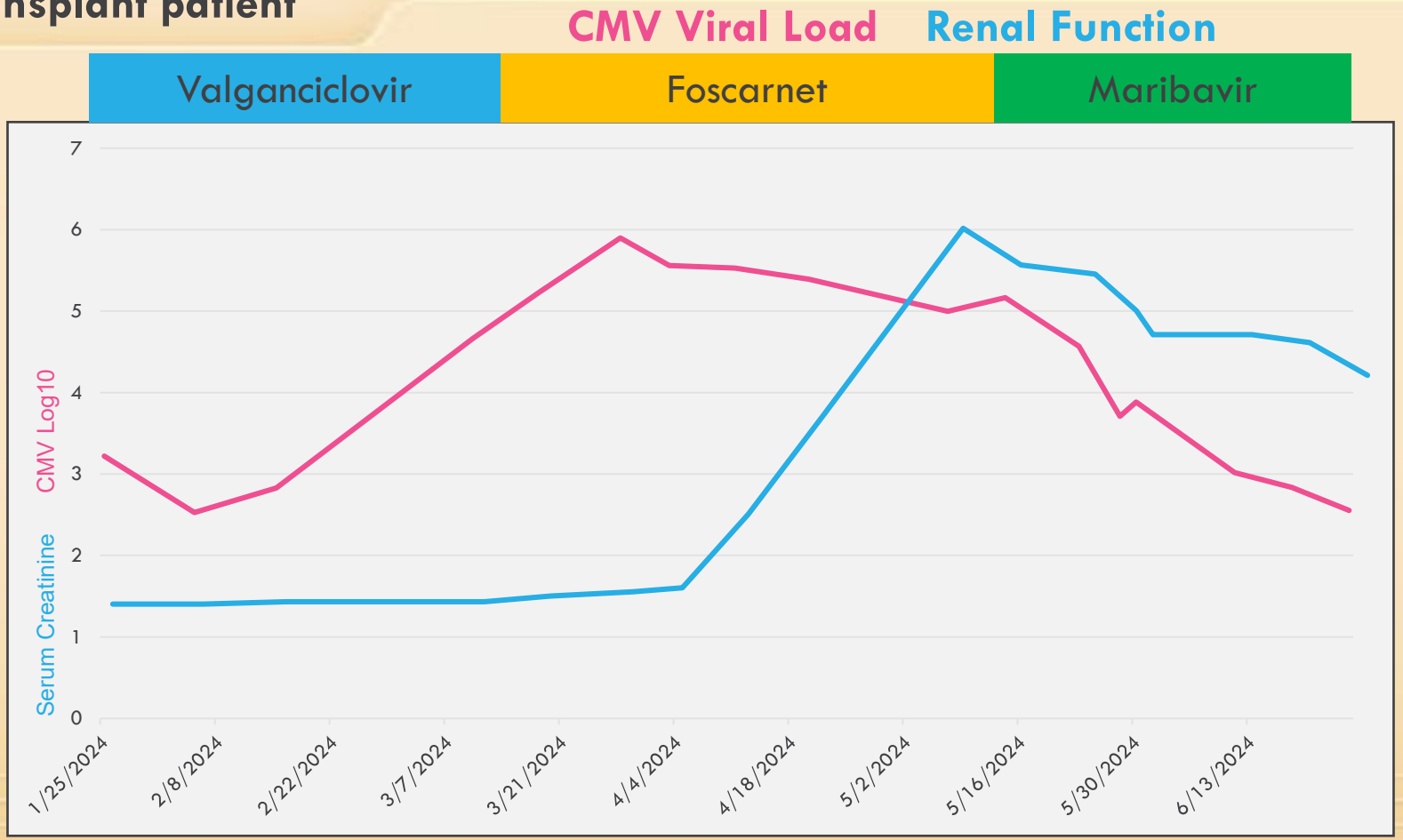
Patient Case 3: 64-year-old male heart transplant patient

- Unfortunately, creatinine increased to 6 mg/dL after 5 weeks of foscarnet
- Changed to maribavir when CMV PCR Log_{10} 4.99 (99,400) IU/mL
- Subsequently, downward trend in viral load
- Interestingly, mutation M460I/V displays hypersensitivity to maribavir[1]

1. Chou S, et al. *Antiviral Res.* 2024;222:105792.

Heart Transplant Patient with Multi-Resistant CMV *(cont'd)*

Patient Case 3: 64-year-old male heart transplant patient



Lung Transplant Patient: Starting Therapy with Maribavir

Patient Case 4: 36-year-old female lung transplant patient with rejection

History

- Idiopathic pulmonary arterial hypertension
- Underwent bilateral lung transplant
  - CMV D+/R-
  - Recurrent rejection treated with steroids while on prophylactic dosing VGCV
  - Asymptomatic
  - Medications include tacrolimus, prednisone, azithromycin, posaconazole, TMP SMX

Labs

- WBC 2.7 cells/µL (consistently<3)
- sCr 1.14 mg/dL

	CMV IU/mL	LOG 10 CMV
Latest Ref Rng		LogIU/mL
1/16/2024 8:11 AM	187	2.3
1/25/2024 9:06 AM	Not Detected	
2/1/2024 8:50 AM	55	1.7
2/8/2024 12:00 AM	ND (whole blood)	
2/9/2024 9:21 AM	Not Detected (BAL)	
2/14/2024 12:00 AM	ND (whole blood)	
2/22/2024 8:59 AM	292	2.5
2/29/2024 8:14 AM	485	2.7
3/6/2024 12:00 AM	3273 (whole blood)	
3/8/2024 8:34 PM	799	2.9
3/14/2024 11:56 AM	5,240	3.7

Lung Transplant Patient: Starting Therapy with Maribavir *(cont'd)*

Patient Case 4: 36-year-old female lung transplant patient with rejection

- Considerations when initiating therapy
  - Symptoms
  - CBC, eGFR
  - CMV viral load (level of CMV DNAemia)
  - Risk of resistance to GCV/VGCV
  - Drug interactions

Latest Ref Rng	CMV IU/mL	LOG 10 CMV LogIU/mL
1/16/2024 8:11 AM	187	2.3
1/25/2024 9:06 AM	Not Detected	
2/1/2024 8:50 AM	55	1.7
2/8/2024 12:00 AM	ND (whole blood)	
2/9/2024 9:21 AM	Not Detected (BAL)	
2/14/2024 12:00 AM	ND (whole blood)	
2/22/2024 8:59 AM	292	2.5
2/29/2024 8:14 AM	485	2.7
3/6/2024 12:00 AM	3273 (whole blood)	
3/8/2024 8:34 PM	799	2.9
3/14/2024 11:56 AM	5,240	3.7

Lung Transplant Patient: Starting Therapy with Maribavir *(cont'd)*

Patient Case 4: 36-year-old female lung transplant patient with rejection

- Considerations when initiating therapy
  - Symptoms – NONE
  - CBC, eGFR – Slightly above baseline
  - CMV viral load (level of CMV DNAemia) – LOW ($<\log_{10} 5$)
  - Risk of resistance to GCV/VGCV – HIGH
  - Drug interactions – MANAGEABLE

Latest Ref Rng	CMV IU/mL	LOG 10 CMV LogIU/mL
1/16/2024 8:11 AM	187	2.3
1/25/2024 9:06 AM	Not Detected	
2/1/2024 8:50 AM	55	1.7
2/8/2024 12:00 AM	ND (whole blood)	
2/9/2024 9:21 AM	Not Detected (BAL)	
2/14/2024 12:00 AM	ND (whole blood)	
2/22/2024 8:59 AM	292	2.5
2/29/2024 8:14 AM	485	2.7
3/6/2024 12:00 AM	3273 (whole blood)	
3/8/2024 8:34 PM	799	2.9
3/14/2024 11:56 AM	5,240	3.7

Lung Transplant Patient: Starting Therapy with Maribavir *(cont'd)*

Patient Case 4: 36-year-old female lung transplant patient with rejection

Patient started on Maribavir 400 mg q12

	CMV IU/mL	LOG 10 CMV	CMV (copies/mL)
Latest Ref Rng & Units		LogIU/mL	
3/14/2024	5,240	3.7	SPECIMEN TYPE: Plasma...
3/21/2024	1,220	3.1	SPECIMEN TYPE: Plasma...
3/27/2024	134	2.1	SPECIMEN TYPE: Plasma...
3/29/2024	546	2.7	SPECIMEN TYPE: Bronchoalveolar lavage (BAL)...
4/1/2024	47	1.7	SPECIMEN TYPE: Plasma...
4/8/2024	<35	<1.5	SPECIMEN TYPE: Plasma...

- Considerations for discontinuing therapy
  - ? time-based versus lab test-based
  - If requiring negative DNAemia, how many are necessary?
- Is there guidance about secondary prophylaxis?

Audience Q&A